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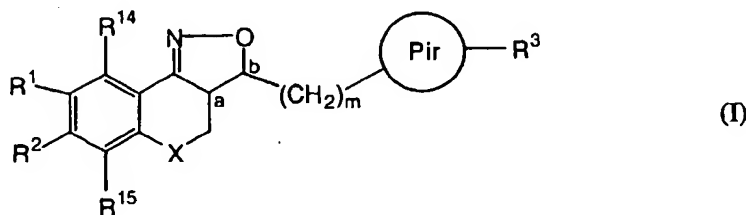
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(54) Title: C6- AND C9-SUBSTITUTED '4, 3-C' ISOXAZOLINE DERIVATIVES AND THEIR USE AS ANTI-DEPRESSANTS



(57) Abstract: The invention concerns substituted tricyclic isoxazoline derivatives, more in particular tricyclic dihydrobenzopyr-  
ranoisoxazoline, dihydroquinolinoisoxazoline, dihydronaphthalenoisoxazoline and dihydrobenzothiopyranoisoxazoline derivatives  
substituted on at least one of the C6- and C9-positions of the phenylpart of the tricyclic moiety with a selected radical, according  
to Formula (I) wherein X = CH<sub>2</sub>, N-R<sub>14</sub>, S or O, R<sub>14</sub>, R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are certain specific substituents, with the  
proviso that at least one of R<sub>14</sub> and R<sub>15</sub> is not hydrogen, Pir is preferably an optionally substituted piperidinyl or piperazinyl  
radical and R<sub>3</sub> represents an optionally substituted aromatic homocyclic or heterocyclic ring system including a partially or com-  
pletely hydrogenated hydrocarbon chain of maximum 6 atoms long with which the ring system is attached to the Pir radical and  
which may contain one or more heteroatoms selected from the group of O, N and S; a process for their preparation, pharmaceutical  
compositions comprising them and their use as a medicine, in particular for the treatment of depression, anxiety, movement disor-  
ders, psychosis, Parkinson's disease and body weight disorders.. The compounds according to the invention have surprisingly been  
shown to have a serotonin (5-HT) reuptake inhibitor activity in combination with additional α<sub>2</sub>-adrenoceptor antagonist activity  
and show a strong anti-depressant activity without being sedative. The invention also relates to novel combination of isoxazoline  
derivatives according to the invention with one or more other compounds selected from the group of antidepressants, anxiolytics,  
anti-psychotics and anti-Parkinson's disease drugs to improve efficacy and/or onset of action.

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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,  
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/09532

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D498/04 A61K31/424 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 07262 A (MERCK SHARP & DOHME ; COLLINS IAN JAMES (GB); LEESON PAUL DAVID (GB) 16 March 1995 (1995-03-16) page 10	1-5, 7-14
A	WO 97 25317 A (HOECHST MARION ROUSSEL INC) 17 July 1997 (1997-07-17) claim 1	1-5, 7-17
T	WO 02 066484 A (LANGLOIS XAVIER JEAN MICHEL ; BAKKER MARGARETHA HENRICA MARI (BE);) 29 August 2002 (2002-08-29)	1-5, 7-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*S\* document member of the same patent family

Date of the actual completion of the international search

23 January 2004

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02/02/2004

Name and mailing address of the ISA

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Authorized officer

Grassi, D

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 03/09532

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 6, 7-14 (part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 6, 7-14 (part)

Present claim 6 relates to a compound defined by reference to a desirable property, namely the degradability in vivo to yield a compound of claims 1-5.

The claim covers all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for compounds according to claims 1-5. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds defined by a chemical formula.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/09532

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